Streamlining of prehospital stroke management: the golden hour

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Thrombolysis with alteplase administered within a narrow therapeutic window provides an effective therapy for acute ischaemic stroke. However, mainly because of prehospital delay, patients often arrive too late for treatment, and no more than 1–8% of patients with stroke obtain this treatment. We recommend that all links in the prehospital stroke rescue chain must be optimised so that in the future more than a small minority of patients can profit from time-sensitive acute stroke therapy. Measures for improvement include continuous public awareness campaigns, education of emergency medical service personnel, the use of standardised, validated scales for recognition of stroke symptoms and for triaging to the appropriate institution, and advance notification to the receiving hospital. In the future, use of telemedicine technologies for interaction between the emergency site and hospital, and the strategy of treatment directly at the emergency site (mobile stroke unit concept), could contribute to more efficient use of resources and reduce the time taken to instigate treatment to within 60 min—the golden hour—of the onset of the symptoms of stroke.

Introduction

Stroke is the most frequent cause of permanent disability in adults and one of the most frequent causes of death. In addition to substantial individual suffering, stroke results in enormous costs to society. Intravenous thrombolysis with alteplase is an effective treatment for acute ischaemic stroke, as shown in several randomised and placebo-controlled multicentre studies. The approved time window for stroke treatment after the onset of symptoms ranges from 3 h to 4·5 h in various countries. However, even within this time window, the benefit of treatment strongly decreases as time passes (the so-called time-is-brain concept). The same time-sensitivity can be expected with novel endovascular treatment options. The number needed to treat with intravenous alteplase for a good outcome, defined as a modified Rankin score of 0–1, has been calculated at 4·5 if treatment is initiated within 1·5 h after the onset of symptoms. This number doubles to 9 if treatment is initiated between 1·5 h and 3·0 h after symptom onset, and reaches 14–1 if treatment is delivered between 3·0 h and 4·5 h after onset. For every minute a large- vessel stroke goes untreated, an estimated maximum of 1·9 million neurons and 14 billion synapses are potentially lost, suggesting that even small differences in time to reperfusion could produce clinically relevant differences.

In this Review of prehospital stroke management we emphasise that all links in the prehospital stroke rescue chain must be optimised so that in the future more than a small minority of patients can profit from time-sensitive acute stroke therapy.

Prehospital stroke management to reduce treatment delay

Before alteplase can be delivered, a complex diagnostic work-up (including neurological examination, imaging, and laboratory analysis) is necessary for exclusion of haemorrhage, diseases mimicking stroke, and other contraindications. This work-up consumes crucial time, often precluding treatment within the approved therapeutic window. Although in some experienced specialised centres administration of intravenous alteplase to 20–30% of patients with ischaemic stroke within 3 h is possible, in clinical reality, across the entire population of patients with stroke, this treatment can be given to only a small minority (1–8%) of such patients.

The main medical problem related to the underuse of available stroke treatment is encountered to a large extent before the patient reaches the doors of the hospital, because most patients arrive too late to be considered for recanalising treatments. Previous studies showed that only 15–60% of patients with stroke arrived at the hospital within 3 h after the onset of symptoms, and only 14–48% arrived within 2 h. The strength of such data is, however, limited by the selective evaluation of patients for whom symptom onset times were available. Importantly, data from the Get with the Guidelines stroke programme showed that the proportion of patients with ischaemic stroke who arrived at hospital within 2 h of symptom onset did not increase significantly from 2003 to 2009. In non-western countries this delay is even more pronounced.

After a previous focus on options to prolong the temporal treatment window, current efforts to solve the problem of the underuse of alteplase are centred on more efficient use during the first hours after stroke. A recent simulation of the net benefit of extending the time window for thrombolysis with alteplase was done on the basis of data from 3830 patients registered in the Safe Implementation of Treatment in Stroke International Stroke Thrombolysis Registry (SITS-ISTR). The results of this simulation suggested that, in view of the lower efficacy of thrombolysis at later timepoints and the so-called deadline effect (a relaxation of the subjectively perceived urgency to treat patients when more time remains), a reduction of start of treatment times by 8 min (compared with the present mean time to start of
treatment after symptom onset) would confer a population benefit as large as that conferred by extension of the time window from 3·0 h to 4·5 h.19

Prehospital processes are determined in large part by the behaviour of the patients and bystanders and by that of the emergency medical service (EMS) personnel.19

Role of the patients
Delay in seeking medical attention
Delay in seeking medical attention after the onset of stroke symptoms is an important reason for the underuse of thrombolytic therapies.8–46 Reported delays in seeking treatment range from 38 min to 4 h.41–45 Between 24% and 54% of patients with stroke do not call for help within 1 h,41,46–48 and many do not seek medical care at all. Reports suggest that only 38–65% of patients use EMS.41,42

Much evidence suggests, however, that the use of EMS is a crucial variable to reduce prehospital delay.46,49–49 For example, among the 13894 patients in the North Carolina Collaborative Stroke Registry,28 the use of EMS, rather than other modes of transportation, was a strong predictor of hospital arrival within 2 h of onset of symptoms (odds ratio [OR] 2·3, 95% CI 1·9–2·8). By contrast, inappropriate care-seeking behaviour, such as using a private vehicle, visiting a general physician, or adopting a wait-and-see attitude, contributes to increased delay.50,45,51,52

Various determinants of appropriate care-seeking behaviour have been identified. Among the demographic factors examined, women are better than men at recognising stroke symptoms49 and highly educated, higher income people are better informed about stroke symptoms and are more likely to seek medical care.53,54 The results of several studies suggest that delays in seeking treatment are longer among members of minority ethnic groups.55,56 Social factors, such as not living alone and the presence of bystanders, are associated with reduced delays.45,49–50 Regarding medical history, the effect of a patient having already had a stroke is unclear, but it has been reported that delays are shorter when the caller has a family history of stroke than when he does not.45 Conceivably, the severity of stroke also strongly affects care-seeking behaviour. Severe symptoms, such as disturbed consciousness, speech problems, and severe motor impairment, or a sudden onset of stable deficits,48 are associated with short prehospital times.45,51,52 Finally, psychological factors such as fear of disease and fear of hospital contribute to detrimental wait-and-see behaviour.46,48

Stroke education campaigns
Early recognition and rapid response to the symptoms of stroke by patients and witnesses are crucial to improve access to thrombolysis and ultimately improve outcome after stroke.45,46 Several studies in various countries41–47 have evaluated the effect of educational campaigns on stroke knowledge and care-seeking behaviour. Although many educational campaigns have been successful in raising awareness of the signs and symptoms of stroke, they have had little effect on actual behaviour in response to stroke.48,49 suggesting that, contrary to the commonly held premise, increased knowledge of stroke does not necessarily translate into an increase in appropriate actions.60,61 Furthermore, many studies assessed only a measure of change in people’s intention to act should the situation arise, rather than an actual change in their behaviour in an actual emergency.

The few studies that have examined the effect of stroke educational campaigns on alteplase treatment rates and reduction of time from symptom onset to hospital admission have yielded inconsistent findings. Before alteplase was licensed, Alberts and colleagues62 evaluated the effect of a combined 3-month mass media intervention targeting both community members and health-care professionals on recruitment to a trial of alteplase. In the 12 months after the campaign, the number of patients with stroke who arrived at the hospital within 24 h of symptom onset increased from 37% to 86% (p<0·0001). A further public campaign aimed to increase stroke knowledge and improve stroke response, undertaken as part of the NINDS rt-PA Stroke Trial,63 resulted in a fall from 3·2 h to 1·5 h (p<0·05) in the mean time to hospital arrival during the intervention period. Morgenstern and coworkers64 implemented two 15-month interventions targeting community members and professionals with the aim of increasing the proportion of patients treated with alteplase. Selected matched hospitals in a different area served as a control community. Time to hospital arrival decreased in both communities, but the use of alteplase increased only in the intervention community (p=0·01). The increase in treatment rates was sustained beyond the intervention period, suggesting that its effect was exerted primarily on health professionals rather than on community members.64 A 12-month community and health professional stroke education intervention in Houston, TX, USA, increased monthly stroke admissions from 74 to 89 (p<0·001) and increased the diagnostic accuracy of paramedics.65 During the intervention, an increase in alteplase treatment rates was noted in four hospitals and a decrease was recorded in two hospitals. Paradoxically, however, transport times also increased, from 42–2 min to 45–8 min (p<0·01). In Ontario, Canada, two television-based campaigns66 resulted in a larger number of stroke symptoms remembered (p<0·001) and a larger number of emergency department visits for stroke during the intervention than before (p<0·01). However, awareness of symptoms decreased during the 5-month period after the intervention. In another study, 75720 participants in Berlin, Germany,67 were sent an educational letter explaining stroke symptoms and the importance of calling the EMS. A prehospital time of 3 h or less was achieved by 34% of patients in the intervention group and by 28% of patients in the control group. However, the effect was significant only for women. Finally, a more recent population-based study68 involving
1392 patients with stroke in a multiethnic population in south London, UK, showed no differences in the proportion of patients who arrived at the hospital within 3 h before a media campaign (41%) and after the campaign (45%) and no difference between the two timepoints in rate of alteplase use (before, 17%; after, 16%).

In view of the mixed results of previous educational campaigns in reducing the time between symptom onset and hospital arrival, or in improving thrombolysis treatment rates, an obvious challenge is overcoming the gap between knowledge about stroke and appropriate behaviour in the emergency situation.10,59,60 Several variables are associated with increased success rates for public education campaigns, which will be helpful for the design of future campaigns (panel 1).

Role of the EMS
Educational programmes for EMS personnel
A great potential for optimisation of stroke management lies with the EMS. The structures of EMS are highly variable between countries and even between states or areas of individual countries.90,91 Therefore, generalisation of the results of studies in one setting to other settings is difficult. Fairly good evidence already exists for several factors, such as the effectiveness of educational programmes for EMS personnel, the use of instruments for symptom recognition, priority transport to centres with stroke experience, and algorithms for advance notification of receiving hospitals. By contrast, evidence for or against configuration of the EMS response to acute stroke (physician-based vs paramedic-based response) or the use of novel telestroke technologies is scarce.

The correct identification of stroke symptoms is not trivial: on one hand, symptoms (eg, those related to the posterior circulation) can be difficult to recognise; on the other hand, as many as 20% of presumed stroke symptoms are caused by completely different diseases (so-called stroke mimics). The reported proportion of strokes correctly identified by EMS dispatchers varies between 30% and 83%92,93, a finding that suggests the need for continual educational programmes. Such programmes should include, in addition to medical training, instructions about the use of instruments to recognise stroke, the importance of priority transfer to referral centres with experience in treating stroke, and the prenotification of these centres before the patient arrives. Studies have shown that educational programmes for both EMS dispatchers and personnel led to improved recognition of stroke symptoms, faster stroke management,94,95 and even increases in the rates of thrombolysis.95 EMS personnel should also be aware of the potential to rescue brain tissue when a wake-up stroke is suspected. Although further research on this issue is necessary, and several clinical trials are currently enrolling, triage of patients with suspected wake-up stroke to centres with 24 h per day neuroimaging availability should be considered.

Standardised instruments for symptom recognition
The use by EMS dispatchers during the telephone interview of protocols containing standardised questions, such as the Medical Priority Dispatcher Systems stroke protocol or the Cincinnati prehospital stroke scale, in addition to the usual interrogation, has been shown to increase diagnostic accuracy.96–99 Therefore, existing stroke management guidelines, such as those of the American Heart Association100 or of the European Stroke Organisation,101 recommend the use of standardised instruments by EMS dispatchers.

For EMS personnel in the field, guidelines recommend the use of simple instruments for diagnosis of stroke.100,101 The Cincinnati prehospital stroke scale evaluates the presence or absence of facial palsy, asymmetric arm weakness, and speech disturbance (by having the patient repeat a sentence).102 A study involving 843 patients showed that this scale has a sensitivity of 90% and a specificity of 66% in diagnosis of stroke.103 In addition to analysis of motor weakness, the Los Angeles prehospital stroke screen contains four history items and a blood glucose measurement.104 The

Panel 1: Considerations in the design of public education campaigns
- Researchers must identify the most appropriate targets for campaigns. Elderly people with a low degree of education and members of some minority groups tend to have less knowledge compared with other groups, but are also at high risk of stroke.105,107 Stroke survivors have been selected as an additional specific target group, because their stroke awareness is often poor.107,108 A recent randomised trial108 found that targeting of relatives and neighbours of patients with a history of stroke improved awareness of stroke. Promising strategies include directing of stroke campaigns at medical students and even to children as a medium for spreading information in the at-risk population, as these are the potential next generation of family practitioners, caregivers, or patients.93,94,106
- Researchers need improved understanding of beliefs about stroke and of demographic, cultural, and behavioural factors that influence the decision of patients and bystanders to seek help.93,107
- Researchers must design a simple message that clearly proposes a specific action in response to stroke (such as to call 911, in the USA).106
- Researchers should establish the most appropriate environment for campaigns (such as beauty salons, churches, or waiting rooms)101 and most appropriate media avenues, such as provision of relevant information via online resources.95
- Continuous exposure to the information by regular repeat has been associated with the success of such campaigns.101

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sensitivity (91%) and specificity (97%) of the latter scale are high; however, this scale is more complex and time-consuming than the Cincinnati scale and, thus, is less suited to public education. The face arm speech time (FAST) scale (panel 2) includes three key elements from the Cincinnati scale (facial weakness, arm weakness, and speech disturbance), but assesses language ability by normal conversation with the patient. The authors estimated that the FAST scale has a sensitivity of 79% and a positive predictive value of 78%. This scale is easy to use, not only by EMS personnel but also by community members, and is thus very suitable for public education campaigns.

Most, but not all, studies suggest that these screening guidelines are useful. In the USA the use of the Los Angeles prehospital stroke scale or the Cincinnati prehospital stroke scale is most often recommended, in Australia the Melbourne Ambulance Stroke Screen is most commonly used, and in Europe the FAST scale is most widely used.

Although the use of such scales still represents a compromise between accuracy in the recognition of more complex deficits and practicability in critical emergency situations, their application is an important step in the right direction. However, the use of such standardised instruments varies and is often undocumented in current daily routine, a fact indicating the need for additional research on this issue and further optimisation of the scales.

Priority transport to hospitals with stroke expertise

The emergency priority for stroke should be the same as that for acute myocardial infarction or trauma. Patients greatly benefit from direct transfer to a hospital with stroke expertise and the option for thrombolytic therapy. Having the EMS dispatch office establish an increased priority level for patients with stroke reduces time to arrival at the stroke centre and increases the rates of alteplase use from 10% to 24% (p<0.001) without negatively affecting other medical emergencies, as shown in a recent randomised clinical trial involving 942 patients in Sweden. In specific settings, helicopter transport has been reported to reduce the time to hospital arrival and even to contribute to increased use of thrombolysis therapy. However, air transfer of patients with acute ischaemic stroke who are treated with alteplase does not seem to impart any greater benefit to patient outcomes than does ground transport.

As a very advanced protocol, the previously described city-wide prehospital stroke management protocol in Toronto, ON, Canada, targets all participants in the stroke rescue chain (table). Apart from other measures, such as the use of screening instruments by paramedics or the implementation of an internal hospital stroke code, this protocol includes decision rules for ambulance personnel in determining a destination that bypasses hospitals without stroke expertise; this strategy is enabled by innovative regional collaborations, including agreements among hospitals about later repatriation of the patient. A recent prospective multicentre observational study supports the value of such bypassing protocols by showing that the rates of alteplase use were higher for 283 patients enrolled in an organisational structure in which patients were treated in one stroke centre instead of four community hospitals (22%) than they were for 801 patients who were treated in the nine community hospitals in the control region (14%; OR 1·72, 95% CI 1·22–2·43).

At present, guidelines recommend that EMS personnel transfer patients to the closest institution that provides emergency stroke care. This situation might change, because in addition to intravenous thrombolysis, mechanical recanalisation might become an increasingly important component of the therapeutic arsenal because of its potential for increased efficiency in recanalising large-vessel obstruction. Because mechanical recanalisation is exclusively offered in a few advanced stroke centres with interventional neuroradiologists providing a 24 h a day service (comprehensive stroke centres, neurovascular centres), triaging of patients to stroke centres with various levels of care might become an important issue in the future.

Panel 2: Examples of stroke scales

FAST (the face arm speech time scale for identification of stroke symptoms)

- Facial droop: one side of the face does not move as well as the other
- Arm drift: one arm does not move or drifts downward when held extended
- Speech: patient slurs words, uses the wrong word, or cannot speak at all
- Time: get help immediately

LAMS (Los Angeles motor scale for assessment of stroke severity with high likelihood of large-vessel occlusion)

- Facial droop: one side of the face does not move as well as the other
- Absent 0
- Present 1
- Arm drift
- Absent 0
- Drifts down 1
- Falls rapidly 2
- Grip strength
- Normal 0
- Weak grip 1
- No grip 2
**Prenotification of receiving hospital**

The recommendations of the guidelines of the American Heart Association and the European Stroke Organisation state that EMS personnel should prenotify the receiving hospital that a patient with stroke is on the way. EMS personnel should also provide initial patient data, such as time of onset of symptoms or potential contraindications to alteplase treatment. Such prenotification allows hospitals to prepare and mobilise resources such as imaging devices before the patient arrives. Apart from immediate activation of the hospital stroke team, communication between emergency site and receiving hospital could even allow caregivers to obtain a preliminary informed consent for later treatment. Apart from immediate activation of the hospital stroke team, communication between emergency site and receiving hospital could even allow caregivers to obtain a preliminary informed consent for later treatment. Therefore, prenotificial notification allows hospitals to prepare and mobilise resources such as imaging devices before the patient arrives. Apart from immediate activation of the hospital stroke team, communication between emergency site and receiving hospital could even allow caregivers to obtain a preliminary informed consent for later treatment.

Studies have shown that implementation of advance notification protocols improves quality indicators of later in-hospital stroke management and, in part, improves the rate of alteplase administration. The table summarises the results of the previous interventional studies that investigated the effects of prenotification on symptom-onset-to-door times, door-to-imaging times, door-to-needle times, and rates of alteplase treatment.

These findings from interventional studies are corroborated by observations in several large stroke registries. In the North Carolina Stroke Care Collaborative registry, which includes data from 13 894 patients, time until imaging was assessed as an indicator of the quality of stroke management. Compared with transfer by private vehicle, transport by EMS resulted in more frequent imaging within 25 min, and this result was corroborated by observations in several large stroke registries. In the North Carolina Stroke Care Collaborative registry, which includes data from 13 894 patients, time until imaging was assessed as an indicator of the quality of stroke management. Compared with transfer by private vehicle, transport by EMS resulted in more frequent imaging within 25 min, and this result was corroborated by observations in several large stroke registries.

### Table: Studies of effects of implementation of prenotification protocols

<table>
<thead>
<tr>
<th>Site (number of stroke centres)</th>
<th>Study design</th>
<th>Year</th>
<th>Number of stroke patients with and without intervention</th>
<th>Intervention</th>
<th>Onset-to-door time (min) with and without intervention</th>
<th>Door-to-imaging time (min) with and without intervention</th>
<th>Door-to-needle time (min) with and without intervention</th>
<th>Thrombolysis rates (%)†‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belvis et al‡⁻¹</td>
<td>Barcelona, Spain (1)</td>
<td>Parallel observation</td>
<td>2001–02</td>
<td>39 vs 181</td>
<td>Prenotification</td>
<td>Mean 64·6 (SD 37·8) vs 69·4 (44·6), p=0·542</td>
<td>Mean 35·5 (SD 34·9) vs 120·3 (74·2), p=0·001</td>
<td>Mean 88·1 (SD 25·9) vs 117·8 (30·9), p=0·015</td>
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<tr>
<td>Abdullah et al‡⁻¹</td>
<td>Boston, USA (1)</td>
<td>Before versus after implementation</td>
<td>2004–05</td>
<td>44 vs 74</td>
<td>Prenotification</td>
<td>Median 66 (IQR 42–126) vs 90 (42–174), p=0·42</td>
<td>Median 40 (IQR 25–49) vs 47 (34–81), p=0·01</td>
<td>–</td>
</tr>
<tr>
<td>Quinn et al‡⁻¹</td>
<td>Newcastle, Australia (1)</td>
<td>Before versus after implementation</td>
<td>2005–07</td>
<td>232 vs 205</td>
<td>Prenotification plus bypass protocol</td>
<td>Median 90·5 (IQR 63–185) vs 150 (53–339), p=0·004</td>
<td>–</td>
<td>Median 91·5 (IQR 70–100) vs 89 (85–160), p=0·40</td>
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<tr>
<td>Kim et al‡⁻¹</td>
<td>Busan, Korea (1)</td>
<td>Before versus after implementation</td>
<td>2006–07</td>
<td>328 vs 678</td>
<td>Prenotification plus in-hospital reorganisation</td>
<td>Mean 109·4 (SD 49·4) vs 69·5 (36·4), p&lt;0·01*</td>
<td>–</td>
<td>Mean 34·8 (SD 19·7) vs 48·6 (23·3), p=0·01</td>
</tr>
<tr>
<td>Gladstone et al‡⁻¹</td>
<td>Toronto, Canada (3)</td>
<td>Before versus after implementation</td>
<td>2004–05</td>
<td>290 vs 217</td>
<td>Prenotification plus EMS screening tool, ambulance destination decision rule with bypass protocol</td>
<td>Median 63·3 (IQR 30–90) vs 46·7, p=0·83</td>
<td>–</td>
<td>Median 83·3 (IQR 30–128) vs 79·7, p=0·007</td>
</tr>
<tr>
<td>O’Brien et al‡⁻¹</td>
<td>Gosford, Australia (1)</td>
<td>Before versus after implementation</td>
<td>2006–08</td>
<td>115 vs 67</td>
<td>Prenotification plus prehospital assessment tool, bypass protocol, in-hospital reorganisation</td>
<td>Mean 76 vs 59, p=0·18†</td>
<td>Mean 19 vs 49, p=0·004‡</td>
<td>Mean 56 vs 102, p=0·001†</td>
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<tr>
<td>Casolla et al‡⁻¹</td>
<td>Lille, France (1)</td>
<td>Parallel observation</td>
<td>2008–11</td>
<td>191 vs 56</td>
<td>Prenotification</td>
<td>Median 81 (IQR 61–120) vs 97 (49–144), p=0·628</td>
<td>Median 27 (IQR 14–35) vs 36 (30–58), p=0·01</td>
<td>Median 49 (IQR 39–62) vs 63 (51–97), p=0·003</td>
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**EMS=emergency medical services. *Only patients treated with alteplase were included. †SD not indicated. ‡Rates compared with standard of care at each location.**

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**Thrombolysis rates (%)**

- 19% vs 4·5%, p=0·003
- 41% vs 21%, p=0·04
- 21·4% vs 4·7%, p=0·001
- 14·3% vs 6·5%
- 23·4% vs 9·5%, p=0·01
- 19% vs 7%, p=0·03
- 31% in 2011, no earlier rates specified
paramedic-based EMS response when acute stroke is suspected. The responders usually meet at the emergency site.

In the physician-based emergency medical services (EMS) response, a physician is dispatched along with the normal paramedic-based response to stroke, which is used in countries such as the USA, the UK, the Netherlands, and Sweden, focuses on increasing the speed of patient transfer to the hospital, even though less expertise might be available at the emergency site (the scoop and run concept). The use of a physician-based EMS response to stroke, which is used in countries such as France, Finland, Germany, and Poland, aims to increase the level of competence of personnel at the emergency site, even though additional delay might occur (the stay and play concept). In the physician-based EMS response, a physician is dispatched with the normal paramedic-based response when the EMS dispatcher suspects that the patient has had an acute stroke. This practice is most often realised in the form of a rendezvous system that describes the separate arrival of the physician and the paramedics at a meeting point, usually the emergency site (figure 1). Which EMS configuration is more effective in delivering acute stroke treatment and in triaging patients with stroke remains uncertain.

**Future directions in prehospital acute stroke management**

**Use of ambulances as clinical laboratories for research on stroke treatments**

Interest is increasing in diagnostic and therapeutic approaches for use in the prehospital phase of stroke management; such approaches might allow responders to reach the patient at a time when the chance of rescuing ischaemic brain tissue is highest. Several ambulance-based studies have been done or are underway on topics including diagnostic measures such as ultrasound and electrical impedance tomography for detection of haemorrhage and therapeutic approaches such as neuroprotection or adjustment of physiological variables. Paramedics have made valuable contributions to such studies.

**Telemedicine-based communication between EMS and hospital personnel**

Telemedicine technologies have great potential to supply expertise from the hospital to the personnel at the emergency site and patient-relevant information to the receiving hospital. So far, studies have shown the reliability of telemedicine-based interaction between rural hospitals and stroke centres. Thus, non-specialised hospitals have the option to obtain guidance from high-level stroke centres via systems with the ability to provide two-way real-time audiovisual conferencing and sharing of images.

The results of several trials have shown not only the reliability and safety of remote clinical decision making but also its positive effects on thrombolysis rates and clinical outcome. The Telemedical Pilot Project for Integrative Stroke Care (TEMPiS) project involved 3122 patients, 63% of whom were treated in the network hospitals. After 3 months, 44% of patients treated in network hospitals and 54% of patients treated in control hospitals had a poor outcome (p<0.0001). A recent study also reported the feasibility of teleradiology assessments between hospitals using smart phones. From the cost-effectiveness perspective, a telestroke network between hospitals could increase the number of patients discharged home and could reduce the costs borne by the network hospitals.

An open question is whether patients treated via telemedicine should remain in the local hospital or whether they should be referred to the stroke centre, where they could benefit from treatment in a stroke unit. Although two recent retrospective analyses showed that telemedicine-assisted thrombolysis followed by

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**Figure 1: Paramedic-based (A) and physician-based (B) EMS configuration**

In the physician-based emergency medical services (EMS) response, a physician is dispatched along with the normal paramedic-based EMS response when acute stroke is suspected. The responders usually meet at the emergency site.
transfer to a stroke centre is feasible and safe, the clinical value of this so-called drip-and-ship concept still remains to be verified by prospective controlled studies. By contrast with telemedical interaction between two hospitals, telemedical transmission of such data from the ambulance in the field to the stroke centre is still a challenge. Highly innovative telemedicine concepts that provide neurologists with real-time visual access to the results of a neurological examination done during transport to the hospital were elaborated more than a decade ago. However, the lack of reliability of transport to the hospital were elaborated more than a decade ago. However, the lack of reliability of telemedicine technologies resulting from temporary dropouts and local unavailability of mobile networks is still an unresolved problem that impairs the use of such technology in clinical practice. Two recent studies of the feasibility of prehospital teleconsultation in actual stroke situations or in simulated scenarios found that telecommunication was impaired because of system dropouts in three of 18 missions in one study and in 18 of 30 missions in the other. Because of the great potential of these technologies, the American Heart Association has recommended further research into the use of such systems.

As an intermediate step towards telemedicine-based interaction between EMS and hospital personnel, some studies have shown the feasibility of transmission during patient transport to the receiving hospital of initial structured patient information via personal digital assistants or smart phones.

Prehospital stroke treatment
To ensure that more than 1–8% of patients receive state-of-the-art treatment, stroke management must be reconfigured. One strategy that substantially reduces the time to treatment is the provision of diagnosis and treatment directly at the emergency site (the mobile stroke unit concept; figure 2). This strategy, which was first proposed in 2003 and gradually developed until shown to be feasible in 2010, is based on the use of a normally equipped ambulance (the mobile stroke unit) that also includes a small CT scanner (CERETOM, Neurologica, Boston, MA, USA) for CT, CT angiography, and CT perfusion; a point-of-care laboratory system for all laboratory tests recommended for the approval of alteplase administration; and a teleradiological and teleradiological connection to the hospital. Apart from prehospital thrombolysis, prehospital diagnostic work-up, including CT angiography, allows triaging of patients with large-vessel occlusion to centres with 24 h per day availability of endovascular stroke treatment. In addition to prehospital thrombolysis, prehospital diagnostic work-up, including CT angiography, allows triaging of patients with large-vessel occlusion to centres with 24 h per day availability of endovascular stroke treatment. Prehospital stroke treatment is the comparator. Light green bars show interventional studies, and dark green bars show registries.

Figure 2: Strategies of acute stroke management
(A) Conventional in-hospital stroke treatment. (B) Optimised in-hospital stroke treatment, including hospital bypass protocols, prenotification to the receiving hospital, and in-hospital reorganisation. (C) Prehospital stroke treatment. As an intermediate step towards telemedicine-based interaction between EMS and hospital personnel, some studies have shown the feasibility of transmission during patient transport to the receiving hospital of initial structured patient information via personal digital assistants or smart phones.

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Figure 3: Comparison of median times between symptom onset and injection of alteplase achieved by the strategy of prehospital stroke treatment with those reported in previous interventional studies and large stroke treatment registries
shorter than all other reported time limits for stroke management. Figure 3 shows a comparison of symptom-onset-to-needle times achieved by this strategy with those achieved in previous interventional studies and registries.

The time until therapy decision obtained by prehospital stroke treatment also contrasts with the door-to-needle times recommended by existing stroke management guidelines of 60 min,106,105 or the much larger intervals that are still clinical reality nowadays.20,21

However, no overall improved clinical outcome or change in number of patients deemed eligible for alteplase could be detected, because the trial was not sufficiently powered for statistical analysis of these secondary endpoints. Therefore, the medical efficacy and also the best setting of prehospital stroke treatment must be established by future studies. Although some arguments suggest that increased allocation of resources during the golden hour of stroke could save the costs expended for long-term after-stroke care, the cost-effectiveness of this strategy also remains to be proven. Currently, several centres are further investigating the mobile stroke unit concept.24

The concept of prehospital stroke diagnosis and treatment could integrate future diagnostic (eg, biomarkers or other imaging and image analysis techniques) and therapeutic (eg, sonothrombolysis,25 strategies to limit bleeding, or neuroprotectors26) and could be adapted to local requirements regarding staffing.

Conclusion
This Review clearly shows that every link in the prehospital stroke rescue chain matters and must be further studied for potential improvements. Further research is needed to establish the most effective public awareness programmes that can affect behaviour in an actual emergency situation. Guideline-recommended measures, such as ongoing EMS education, use of stroke recognition scales, triage to hospitals with stroke expertise, and advance notification to the receiving hospitals, should be followed. Furthermore, novel technologies could become relevant in the future, such as telemedicine-based interaction between the EMS and hospital teams, or the mobile stroke unit concept. Stroke physicians should be engaged not only in the in-hospital phase, but also in the prehospital phase of acute stroke management. Together, with the best possible adherence to currently existing recommendations and with novel options that could become available in the future, the golden hour of stroke could be used much more efficiently than it is used today, thereby enabling more than a small minority of patients to receive state-of-the-art stroke treatment.

Contributors
All authors contributed to the literature search, manuscript writing, review, and critique.

Conflicts of interest
We declare that we have no conflicts of interest.

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